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EXAMINER	
BUNNER, BRIDGET E	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/762,154	NEZU ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-11,13,16-27 and 29-36* is/are pending in the application.

4a) Of the above claim(s) *26 and 33-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-11,13,16-25,27,29-32 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *8-11, 13, 16-27, 29-36* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 June 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/521,195.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/23/07; 12/22/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 23 February 2007 has been entered in full. Claims 11, 13, 20, 25 are amended. Claims 1-7, 12, 14-15, and 28 are cancelled. Claims 29-36 are added.

This application contains claim 26 drawn to an invention nonelected with traverse in the reply filed on 12 June 2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Newly submitted claims 33-35 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The previously examined claims (directed to an isolated nucleic acid molecule; Invention I) and the newly submitted claims (directed to a method of screening compounds comprising utilizing the nucleic acid molecule; herein termed Invention "III") are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case, the nucleic acid molecule can be used in materially different processes, such as DNA purification or gene therapy. The distinct inventions require separate, distinct, and non-coextensive searches. As such, it would be burdensome to search the inventions of Groups I and "III" together.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution

on the merits. Accordingly, claims 33-35 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 8-11, 13, 16-25, 27, 29-32, and 36 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The objections to the specification at pg 2-3 of the previous Office Action (23 August 2006) are *withdrawn* in view of the amended specification and title (23 February 2007).

2. The rejection of claims 12, 20, and 25 under 35 U.S.C. § 112, second paragraph as set forth at page 3 of the previous Office Action (23 August 2006) is *withdrawn* in view of cancelled claim 12 and amended claims 20 and 25 (23 February 2007).

3. The rejection of claims 8-25 and 27 under 35 U.S.C. § 102(a) as set forth at pages 14-15 of the previous Office Action (23 August 2006) is *withdrawn* in view of the translation of Applicant's foreign priority papers (23 February 2007).

4. The rejection of claim 11 under 35 U.S.C. § 102(b) as set forth at page 15 of the previous Office Action (23 August 2006) is *withdrawn* in view of the amended claim (23 February 2007).

5. The information disclosure statements submitted on 22 December 2006 and 23 February 2007 have been considered.

Sequence Compliance

6. The Applicant's response to the Sequence Listing Requirements under 37 CFR §1.821 (23 February 2007) has been considered and is found persuasive. Therefore, the requirements set forth at page 2 of the previous Office Action (23 August 2006) are *withdrawn.*

Claim Rejections - 35 USC § 101 and 35 USC § 112, first paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 8-11, 13, 16-25, 27, 29-32, 36 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility. Novel biological molecules lack well established utility and must undergo extensive experimentation. The basis for this rejection was set forth for claims 8-25 and 27 at pages 4-8 of the previous Office Action (23 August 2006).

The claims are directed to an isolated nucleic acid encoding a polypeptide comprising an amino acid sequence at least 70% identical to SEQ ID NO: 1, wherein the polypeptide is a transporter of an organic cation. The claims are also directed to an isolated nucleic acid encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 1, with up to 30 consecutive amino acid substitutions, wherein the polypeptide is a transporter of an organic cation. The claims recite an isolated nucleic acid comprising a strand that hybridizes under stringent conditions to a probe, the sequence of the probe consist of the complement of SEQ ID NO: 2. The claims also recite vectors, cultured host cells, and a method of producing a polypeptide.

Applicant's arguments (23 February 2007), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) At page 10 of the Response, Applicant argues that the asserted utilities are specific because Applicant has not merely hypothesized that the claimed nucleic acids and their encoded proteins "may be useful" in a general sense. Applicant contends that the specification teaches why these particular nucleic acids and their encoded proteins have specific uses, and then goes on to demonstrate the specific uses. Applicant submits that the specification asserts utility of the nucleic acids in expressing proteins that function as organic transporters, as measured by their transport activity with organic cations, such as TEA, carnitine, mepyramine, and quinidine. Applicant also argues that the asserted utility to design drugs that are transported by these encoded proteins is based on the observed affinity of the organic cation transporter proteins for certain types of drugs, such as actinomycin D, which are specific in their affinity for and absorbability by organic transporter proteins.

Applicant's arguments have been fully considered but are not found to be persuasive. Although the specification of the instant application teaches that the hOCTN1 polypeptide transports organic cations, the instant specification does not teach any physiological significance or functional characteristics of the OCTN1 polynucleotide (SEQ ID NO: 2) or polypeptide (SEQ ID NO: 1). The specification also does not disclose any methods or working examples that indicate the polynucleotides and polypeptide of the instant invention are involved in any specific activity. There is no biological activity, phenotype, disease or condition, binding partner, or any other specific feature that is disclosed as being associated with OCTN1. Applicant's asserted utility to design drugs that are transported by these encoded proteins is not specific or substantial.

Such assays can be performed with any transporter polypeptide and nucleic acid. Nothing is disclosed about how the transporter or a cell expressing the transporter is affected by the drugs. Additionally, the specification discloses nothing specific or substantial for the drugs designed in this method. Since this asserted utility is also not presented in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

It is noted that the post-filing date reference of Tamai et al. (FEBS Letters 419 : 107-111, 1997; cited previously), which discloses an isolated nucleic acid encoding the organic transporter protein comprising the amino acid sequence of SEQ ID NO: 1 of the instant application, states that OCTN1 "was found in several human cancer cell lines as well as in normal kidney, bone marrow and trachea, although its physiological role in these tissues remains to be established. Further studies, including subcellular localization using antibody and elucidation of the mechanism of the pH dependence and metabolic energy-sensitive activity, as well as the substrate specificity, are needed to establish the physiological importance of this transporter" (page 111, column 2, last paragraph). Hence, although OCTN1 may transport various organic cations, its physiological role remains to be elucidated.

(ii) At the middle of page 10, Applicant states that the asserted utility in developing carcinostatics is based on the observed prevalence of these specific transporter proteins in tumor cells, and their ability to transport carcinostatics such as actinomycin D, etoposide, vinblastine and daunomycin. Applicant argues that the asserted utility in gene therapy also is specific to these organic cation transporters, which, as described in the specification, are implicated in certain pathological conditions such as fatty liver, myocardiopathy, myopathy, and other

conditions caused by hypocarnitinemia (specification at page 16, lines 5-11). Furthermore, the asserted utility as probes to identify additional members of this organic cation transporter family is based on a detailed knowledge of their distinct, specific, sequence and structural features, as described in the specification, and the knowledge regarding sequences that are specific to organic cation transporters of this family, as described in the specification.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, the specification of the instant application only teaches that hOCTN1 is present in a few *cancer cell lines*, such as HeLa S3, K562, SW480, and A549 (page 24, lines 1-21). There is no evidence in the specification or the prior or post-filing art indicating that hOCTN1 is associated with or has altered expression in cancer cells isolated from tissue as compared to a normal control. Although the hOCTN1 protein of the instant application is able to transport carcinostatics, the physiological function of the protein has yet to be determined. Applicant's asserted utility for the development of carcinostatics is not specific or substantial. Such assays can be performed with any polypeptide and nucleic acid. The specification discloses nothing specific or substantial for the carcinostatics developed in this method. Since this asserted utility is also not presented in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

Applicant argues that OCTN1's asserted utility in gene therapy is specific to these organic cation transporters, which are implicated in conditions such as fatty liver, myocardiopathy, myopathy, and other conditions caused by hypocarnitinemia. However, the specification teaches that "[e]specially, since "OCTN2" [not OCTN1] included in the transporter proteins of this invention efficiently transports carnitine, chemotherapy with compounds to

control the activity of "OCTN2" or gene therapy using the "OCTN2", gene is considered to be efficacious against various pathological conditions such as fatty liver, myocardiopathy, myopathy, etc. caused by hypocarnitinemia" (page 16, lines 5-11). The specification is silent with respect to diseases or conditions associated with a mutated, deleted, or translocated OCTN1 gene (SEQ ID NO: 2). In order for a polypeptide or nucleic acid molecule to be useful, as asserted, for diagnosis or treatment of a disease, there must be a well-established or disclosed correlation or relationship between the polypeptide/nucleic acid molecule and a disease or disorder. Significant further experimentation would be required by the skilled artisan to identify such a disease or condition in a subject. Since this asserted utility is also not present in mature form so that it could be readily used in a real world sense, the asserted utility is not substantial. Significant further experimentation would be required of the skilled artisan to identify individuals with such a disease.

Finally, although Applicant indicates OCTN1's asserted utility as a probe to identify additional members of this organic cation transporter family is based on a detailed knowledge of their distinct, specific, sequence and structural features, this utility is not specific or substantial. The specification does not disclose a specific DNA target or nucleic acid region to be utilized as a probe. The instant hOCTN1 gene and protein have not been associated with any diseases and disorders and no physiological activity has been identified. Additionally, the specification discloses nothing specific or substantial for the additional members that can be identified by this method. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

(iii) At page 11 of the Response of 23 February 2007, Applicant submits that the specification teaches how the proteins encoded by the claimed nucleic acids can be used to study the transport of various organic cations, including carcinostatic agents, in cells, and can therefore be used to screen for compounds that are amenable to being transported by these proteins. The screening assays further find use in developing particular carcinostatic agents for different types of cancer, given the distribution of these genes in various tumor cell lines. No further research is necessary to confirm the clear identification and characterization of these genes as encoding organic cation transporter proteins; what is asserted as a utility is their use in assays to identify compounds that might be pharmacologically effective in certain diseases such as cancer (as demonstrated by the distribution of these genes and their expression in cancer tissues), or their use as probes to identify additional members of the family. Such uses as research tools more than adequately satisfy the standard of a "substantial" utility.

Applicant's arguments have been fully considered but are not found to be persuasive. As discussed in the previous Office Action, the instant specification and the post-filing date art do not teach any physiological significance or functional characteristics of the OCTN1 polynucleotide (SEQ ID NO: 2) or polypeptide (SEQ ID NO: 1). The specification also does not disclose any methods or working examples that indicate the polynucleotides and polypeptide of the instant invention are involved in any specific activity. There is no biological activity, phenotype, disease or condition, binding partner, or any other specific feature that is disclosed as being associated with OCTN1. Without any information as to the specific properties of OCTN1, the mere identification of the polypeptide is not sufficient to impart any particular utility to the claimed polynucleotides. As discussed above, the post-filing date study of Tamai et al. (FEBS

Letters 419 : 107-111, 1997), which discloses an isolated nucleic acid encoding the organic transporter protein comprising the amino acid sequence of SEQ ID NO: 1 of the instant application, states that OCTN1 "was found in several human cancer cell lines as well as in normal kidney, bone marrow and trachea, although its physiological role in these tissues remains to be established. Further studies, including subcellular localization using antibody and elucidation of the mechanism of the pH dependence and metabolic energy-sensitive activity, as well as the substrate specificity, are needed to establish the physiological importance of this transporter" (page 111, column 2, last paragraph). Hence, although OCTN1 may transport various organic cations, its physiological role remains to be elucidated.

As discussed in part (ii) above, the specification of the instant application only teaches that hOCTN1 is present in a few *cancer cell lines*, such as HeLa S3, K562, SW480, and A549 (page 24, lines 1-21). There is no evidence in the specification or the prior or post-filing art indicating that hOCTN1 is associated with or has altered expression in cancer cells isolated from tissue as compared to a normal control. Although the hOCTN1 protein of the instant application is able to transport carcinostatics, the physiological function of the protein has yet to be determined. Applicant's asserted utility for the development of carcinostatics is not specific or substantial. Such assays can be performed with any polypeptide and nucleic acid. The specification discloses nothing specific or substantial for the carcinostatics developed in this method. Since this asserted utility is also not presented in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial. Applicant's asserted utility of studying the transport of various organic cations, including carcinostatic agents, in cells, and screening for compounds that are amenable to being transported by these proteins is

not specific or substantial. Such assays can be performed with any polypeptide. The specification discloses nothing specific or substantial for the compounds screened in this method. Since this asserted utility is also not presented in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial. Whereas a scale or a microarray or a gas chromatograph has patentable utility as a research tool, the objects being evaluated with those research tools do not necessarily have patentable utility. In the instant case, the claimed hOCTN1 nucleic acid molecules and encoded polypeptides are not disclosed as having an activity that can be specifically useful. Thus, further research is required to identify or reasonably confirm a specific and substantial utility. MPEP §2107(I)(C) even states that "[l]abels such as "research tool," "intermediate" or "for research purposes" are not helpful in determining if an applicant has identified a specific and substantial utility for the invention". The U.S. Court of Appeals for the Federal Circuit recently addressed the utility requirement in the context of a claim to DNA (see *In re Fisher*, 421 F.3d 1365, 76 USPQ2d 1225 (Fed. Cir. 2005). The Fisher court held that §101 requires a utility that is both substantial and specific. The court held that a "[p]atent application does not satisfy utility requirement of 35 U.S.C. §101 unless it discloses both "substantial" utility for claimed invention, in form of significant and presently available benefit to public, as well as "specific" utility, which is well-defined and particular benefit to public".

(iv) At the bottom page 11 of the Response, Applicant indicates that contrary to Examiner's assertion, the *Brenner* case has no bearing on the facts of the instant application. In contrast to the *Brenner* case, Applicant asserts that the instant application provides nucleic acids and their

encoded proteins have an established biological function, that of an organic cation transporter, and so can be used in a variety of "real world" applications that are specific to these compounds.

Applicant's arguments have been considered but are not found to be persuasive. The instant application is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966). A clone encoding the hOCTN1 amino acid sequence was identified as having significant homology with the known organic cation transporters, OCT1 and OCT2 (specification page 21, lines 1-10). Although the instant specification demonstrates that hOCTN1 transports various organic cations, the physiological role of the hOCTN1 has not been identified. In *Brenner v. Manson*, the court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. §101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

(v) It is noted that at pages 12-13 of the Response, Applicant cites pertinent case law reviewing the legal standard of utility and the Utility Examination Guidelines. The Examiner takes no issue with Applicant's general comments regarding the legal standard for utility.

(vi) At page 13 of the Response, Applicant submits that Applicant has demonstrated a reasonable scientific basis that the asserted utilities are specific and substantial, and in light of the detailed teachings regarding the structure and biological activities of this newly discovered gene family, are credible.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, the credibility of the claimed nucleic acid molecules was not questioned by the Examiner, but the asserted utilities were not specific or substantial for reasons set forth above and at pages 4-8 of the previous Office Action (23 August 2006).

Enablement

8. Claims 8-11, 13, 16-25, 27, 29-32, 36 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. The basis for this rejection was set forth for claims 8-25 and 27 at page 8 of the previous Office Action (23 August 2007).

8a. However, even if the claimed invention is eventually deemed to have a specific and substantial asserted utility or a well established utility, claims 8, 10, 16, 18, 21, 23, 27, 29-31, and 32 would remain rejected under 35 U.S.C. § 112, first paragraph. The basis for this issue was set forth for claims 8, 10-12, 14-16, 18-21, 23-25, and 27 at pages 8-11 of the previous Office Action (23 August 2007). Specifically, the specification of the instant application teaches that mutant proteins obtained by altering the amino acid sequence of the transporter protein by

substitution, deletion, or addition of amino acid residues and are functionally equivalent to those transporter proteins of the invention are included in the invention (pg 9, lines 22-27). However, the specification does not teach any variant, fragment, or derivative of the hOCTN1 polypeptide other than the full-length amino acid sequence of SEQ ID NO:1. The specification also does not teach any variant, fragment, or derivative of the hOCTN1 nucleic acid other than the full-length nucleic acid sequence of SEQ ID NO: 2.

Applicant's arguments (23 February 2007), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) At page 19 of the Response, Applicant asserts that there is no requirement for disclosure of every species within a genus. Applicant indicates that Applicant is entitled to claims commensurate in scope with that which one skilled in the art could obtain by virtue which the applicant has disclosed. At the top of page 20 of the Response, Applicant states that the teachings of the specification are commensurate with the full scope of the claims. Applicant points out that the claims reciting variant sequences all specify that the isolated nucleic acid encodes a polypeptide that is a transporter of an organic cation. Applicant submits at pages 20 and 21 of the Response that the specification (particularly Examples 2 and 3) provides teachings regarding the structure of hOCTN1, including its functional domains, how to alter the nucleic acid encoding hOCTN1 in a manner that produces variants that retain transporter function, the identification of naturally-occurring variants that belong to the hOCTN1 family, how to test the transport activity of the variants, and how to screen for compounds that have an affinity for the transporter proteins.

Applicant's arguments have been fully considered but are not found to be persuasive. The Examiner acknowledges that the instant specification discloses the consensus sequences of sugar transporter and ATP/GTP binding site (Figure 3). However, as discussed in the previous Office Action, certain positions in the polypeptide sequence are critical to the protein's structure/function relationship, e.g., such as various sites or regions directly involved in binding, activity, and in providing the correct three-dimensional spatial orientation of binding and active sites. Applicant has provided little or no guidance beyond the mere presentation of sequence data and the consensus sequences to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the DNA and protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions.

It is noted that a specification may be enabling even though some experimentation is necessary, but the amount of experimentation, however, must not be unduly extensive (MPEP § 2164.06). In the instant case, the specification's general discussion of making and screening for variants (pg 9-11) constitutes an invitation to experiment by trial and error. Undue experimentation would be required by the skilled artisan to generate the infinite number of OCTN1 nucleic acid derivatives, fragments and variants recited in the claims and to screen them for a desired activity. Such trial and error is considered undue. As was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970);

Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991).

(ii) Applicant also contends at page 20 of the Response that the specification provides no less than three other specific examples of organic cation transporter proteins, all with different degrees of homology to hOCTN1, which were discovered as belonging to the hOCTN1 family. Applicant indicates that hOCTN2 (Examples 4, 8 of the specification) is 76% homologous to hOCTN1 and also has organic cation transporter activity. Applicant states that mouse OCTN1 and OCTN2 are cloned and sequenced, as disclosed in the specification.

Applicant's arguments have been fully considered but are not found to be persuasive. Applicant concludes that mOCTN1, hOCTN2, and mOCTN2 are members belonging to the OCTN1 family. However, based upon the disclosure of the instant specification, it appears that hOCTN1 and hOCTN2 may be related transporters, but not variants of one another (species). For example, the specification teaches that hOCTN1 transports organic cations, such as quinidine, mepyramine, TEA, carnitine, actinomycin D, etoposide, vinblastine, and daunomycin (page 31, lines 1-8). On the other hand, OCTN2 transports carnitine and hardly transports TEA (page 32, lines 28-30). Thus, it is clear from the instant specification that OCTN1 and OCTN2 are different transporters that transport different cations.

(iii) At page 22 of the Response, Applicant contends that while it may be true that in some instances a single amino acid substitution can affect the function of a polypeptide, it is also recognized in the art that, for any given protein, many residues can be substituted without

affecting a specified function. Applicant argues that given the detailed knowledge of sequence, structure and function of a protein, one can predictably alter its sequence in a manner that retains function (as exemplified by Applicants' own disclosure of SEQ ID NOS: 1 and 3; hOCTN 1 and hOCTN2), and by the prior art of Bowie et al. (1990) *Science* 247:1306-1310. Applicant points out that at page 1306, lines 12-13, Bowie teaches that "proteins are surprisingly tolerant of amino acid substitutions". Thus, Applicant concludes that one can expect, based on Bowie et al. 's teachings, to find over half (and possibly well over half) of random substitutions in any given protein to result in proteins with full or nearly full activity. Applicant adds that based on Bowie et al. 's teachings, one would predict that even random substitution of residues in SEQ ID NO: 1 will predictably result in a majority of the variants having full or partial transporter activity.

Applicant's arguments have been fully considered but are not found to be persuasive. Although Bowie et al. states that "proteins are surprisingly intolerant of amino acid substitutions", the studies relied upon by Bowie do not examine mutations in receptors or ion transporters. In addition, upon discussing a study carried out the with *lac* repressor, Bowie et al. states "[a]t other positions, no substitutions or only conservative substitutions were allowed" (page 1306, column 2, lines 19-20). In the previous Office Action, Ngo et al. and Wells et al. were cited by the Examiner to emphasize that positions in the amino acid sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. Ngo et al. state that decades of research have failed to produce an efficient algorithm for predicting the structure of a given protein from its amino acid sequence alone (pg 492, 2nd full paragraph). Wells et al. teach that "it is possible to modulate protein function by

mutation at many contact sites" and "to design large changes in function will often require mutation of more than one functional residue" (pg 8509, first paragraph; emphasis added). Wells et al. disclose that more pronounced deviations from simple additivity "can occur when the sites of mutations strongly interact with one another (by making direct contact or indirectly through electrostatic interactions or large structural perturbations) and/or when both sites function cooperatively" (pg 8515, column 2, 3rd full paragraph). For example, the stabilizing interaction between two side chains can be broken with one mutation and if the catalytic functions of two or more residues are interdependent, then a mutation of one residue can alter the functioning of the other(s) (pg 8512, column 2, 2nd full paragraph; pg 8515, column 1, 2nd full paragraph).

The other references were cited by the Examiner (Skolnick et al., Bork 2000, Doerks et al., Smith et al., Brenner et al., Bork 1996) to indicate that the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily

coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Additionally, the Examiner cited references in the previous Office Action that contain numerous examples of transporter families (including SLC22 (OATs, OCTN, etc.) whose members have high homologies yet disparate functions (see for example, Bisson et al., Liang et al., Barrett et al., Koepsell et al. 2003). Thus, the skilled artisan would not be able to determine, without undue experimentation, the structural conformation and function of hOCTN1 variants encompassed by the instant claims based upon linear nucleic acid and amino acid sequences only. One skilled in the art would also not be able to determine, without undue experimentation, the positions in the hOCTN1 protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. The ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is

dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to generate the infinite number of variants and fragments recited in the claims and possibly screen same for activity; the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity; the absence of working examples directed to same; the complex nature of the invention; the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function; and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Written Description

9. Claims 8, 10, 16, 18, 21, 23, 27, 29-31, and 32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection was set forth for claims 8, 10-12, 14-16, 18-21, 23-25, and 27 at pages 11-13 of the previous Office Action (23 August 2007).

Applicant's arguments (23 February 2007), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) It is noted that at pages 14-15 of the Response, Applicant cites pertinent case law reviewing the legal standard of written description. The Examiner takes no issue with Applicant's general comments regarding the legal standard for written description.

(ii) At page 15 of the Response, Applicant argues that the standard for written description has been met. Applicant indicates that the polypeptide having the amino acid sequence set forth in SEQ ID NO: 1, OCTN1, is described and characterized in the specification. Applicant adds that Example 2 describes the cloned human OCTN1 gene was identified as a putative organic cation transporter based on an overall homology of its encoded amino acid sequence of about 34% with the amino acid sequence of known organic cation transporters, OCT1 and OCT2. Applicant states that the hydrophobicity of OCTN1 showed a close resemblance to the domains of OCT1 and OCT2. Applicant argues that hOCTN1 was further used to identify other related organic cation transporter proteins (mOCTN1, hOCTN2, mOCTN2). Applicant concludes that based on this information, there is no question that the specification provides adequate description of the genus of nucleic acids that encode polypeptides with at least 70%, 80%, or 90% identity to the protein encoded by the human OCTN1 gene, and retain the organic cation transporter activity.

Applicant's arguments have been fully considered but are not found to be persuasive. As discussed above in the enablement section, based upon the disclosure of the instant specification, it appears that hOCTN1 and hOCTN2 may be related transporters, but not variants of one another (species). For example, the specification teaches that hOCTN1 transports organic cations, such as quinidine, mepyramine, TEA, carnitine, actinomycin D, etoposide, vinblastine, and daunomycin (page 31, lines 1-8). On the other hand, OCTN2 transports carnitine and hardly

transports TEA (page 32, lines 28-30). Thus, it is clear from the instant specification that OCTN1 and OCTN2 are different transporters that transport different cations. Hence, the description of one human OCTN1 nucleic acid (SEQ ID NO: 2) and one mouse OCTN1 nucleic acid (SEQ ID NO: 23) is not adequate written description of an entire genus of functionally equivalent nucleic acids that encode polypeptides which incorporate all variants, derivatives, and fragments with at least 70%, 76%, 80%, or 90% identity to the amino acid sequence of SEQ ID NO: 2. The instant disclosure fails to provide sufficient description information, such as definitive structural or functional features of the claimed genus of nucleic acid molecules and polypeptides. There is no description of the conserved regions that are critical to the structure and function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function.

Furthermore, in Example 14 of the Written Description Guidelines of the U.S. Patent Office, the claimed protein variants have a high percent sequence identity in combination with a specific functional limitation. In the example, the protein catalyzes the reaction of A→B and thus, methods of generating variants of the protein that have 95% identity and retain its activity are conventional in the art because deletions, substitutions, insertions, and additions of uncritical amino acid residues would not affect the enzyme activity. Moreover, such an enzyme would have a conserved structure that is responsible for the enzyme activity. Thus, it is likely predictable, based upon percent identity, which variant would share the same function. In contrast, in the instant case, claims are directed to such percentage identities as 70%, which is much lower than the 95% recited in Example 14. Furthermore, the specification and the claims

do not disclose the identification of any particular portion of the hOCTN1 structure that must be conserved in order to conserve the required function.

(iii) At pages 16 and 17 of the Response, Applicant asserts that there is detailed description in the specification regarding the sequence, structure and functional domains of hOCTN1 (including consensus motifs defining its transporter function, such as the transmembrane domains, the transporter motif and the ATP/GTP binding motif). The specification further describes exemplary proteins of a broad range of sequence homologies (34% to 76%) to human OCTN1, all of which possess similar structure and function. Therefore, given the description of proteins having homologies from about 34% and higher that show a high degree of structural and functional similarity, there is more than adequate description to evidence possession of the claimed nucleic acids. Applicant adds that one of skill in the art would understand, given the description and specific examples of variants, and given the description in the specification and knowledge of those of skill in the art regarding function-conserving alterations, such as conservative amino acid substitutions in the functional domains, how to alter the organic cation transporter protein hOCTN1 in a manner that retains its functional activity.

Applicant's arguments have been fully considered but are not found to be persuasive. Applicant has not described a representative number of species that have 70%, 76%, 80%, or 90% homology to SEQ ID NO: 1, such that it is clear that they were in possession of a genus of nucleic acids that encode polypeptides functionally similar to SEQ ID NO: 1. Even one skilled in the art could not envision the detailed chemical structure of all or a significant number of encompassed hOCTN1 nucleic acids, and therefore, would not know how to make or use them.

The specification of the instant application only teaches a human OCTN1 nucleic acid of SEQ ID NO: 2 (human polypeptide of SEQ ID NO: 1) and a mouse OCTN1 nucleic acid of SEQ ID NO: 23 (mouse polypeptide of SEQ ID NO: 22). However, the description of two OCTN1 species is not adequate written description of an entire genus of functionally equivalent polypeptides which incorporate all variants, fragments, and derivatives wherein the polypeptide is a transporter of an organic cation.

The broad brush discussion of making and screening for variants in the instant specification does not constitute a disclosure of a representative number of members. No such variants were made or shown to have the same activity as OCTN1. Only the human OCTN1 nucleic acid sequence of SEQ ID NO:2 and the mouse OCTN1 sequence of SEQ ID NO: 23 is disclosed. The specification's general discussion of making and screening for variants constitutes an invitation to experiment by trial and error. Such does not constitute an adequate written description for the claimed variants. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factors present in the claims are a partial structure in the form of a recitation of percent identity and a requirement that the encoded polypeptide is a transporter of an organic cation. There is no identification of any particular portion of the structure that must be conserved in order to conserve the required function or that the described function is truly representative of all members of the claimed

genus. Clearly, such does not constitute disclosure of a representative number of examples of, nor adequate written description for, the claimed genus.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BEB
Art Unit 1647
07 September 2007

Bridget E Bunner

BRIDGET E. BUNNER
PRIMARY EXAMINER